REMARKS/ARGUMENTS

Claims 1, 2, 6, 9, 11, 12, 15, 18, 19, 21, 22, 25, 28, 30-34, 36, 37, 40, 43, 45-48, 51, 54, 180, and 182-186 are pending in this application. No new matter is added.

In support of the remarks and arguments stated *infra*, Applicants have submitted herewith the Declaration of Dr. Dasharatha Reddy.

Rejection under 35 U.S.C. §103(a)

The Examiner has maintained the rejection of claims 1, 2, 6, 9, 11, 12, 15, 18, 19, 21, 22, 25, 28, 30-34, 36, 37, 40, 43, 45-48, 51, 54, 180, 182-186 and 204-209 as being unpatentable over Pardee *et al.* WO 00/61142 ("Pardee") in view of Bodor *et al.* U.S. Patent No. 4,983,586 ("Bodor"). Applicants traverse.

The Examiner has previously stated that the primary reference, Pardee, discloses the use of β-lapachone or analogs and derivatives thereof in combination with G2/M phase drugs, such as paclitaxel (Taxol®), to treat cancer. The Examiner has also stated that Pardee discloses dosage ranges, kits, various methods of administration and that β-lapachone is insoluble in water. However, the Examiner stated that Pardee does not disclose using a beta-cyclodextrin as a solubilizing agent. *See*, March 1, 2004 Office Action at page 3. The Examiner completed the rejection by stating that the secondary reference Bodor teaches that hydroxypropyl-beta-cyclodextrin is useful for solubilizing a wide variety of water-insoluble drugs, particularly anti-neoplastic/anti-tumor agents, by complexation but that Bodor does not disclose β-lapachone or analogs or derivatives thereof. *See*, March 1, 2004 Office Action at pages 3-4. The Examiner asserted that it would have been obvious to have solubilized the water-insoluble, anti-neoplastic/anti-tumor agents of the primary reference (β-lapachone and paclitaxel) by complexing them with hydroxypropyl-beta-cyclodextrin to improve solubility for parenteral administration and that determining the suitability of a given drug for complexation with hydroxypropyl-beta-cyclodextrin is merely a matter of routine. *See*, March 1, 2004 Office Action at page 4.

Motivation

Applicants submit that there is no suggestion or motivation to combine Pardee and Bodor to reach the present invention. Applicants maintain that one of ordinary skill in the art reading Pardee would not be motivated to discover solubilizing carrier molecules to solubilize the disclosed anti-

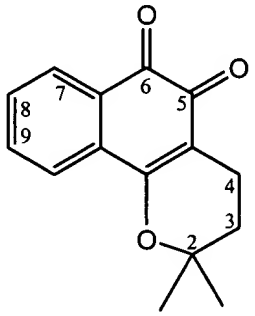
neoplastic/anti-tumor compounds, β-lapachone and paclitaxel, because Pardee teaches that the solubilizing agent, lipiodol, solubilized paclitaxel and solved the long standing problem of β-lapachone insolubility and that these formulations were successful therapeutically in treating cancer *in vivo* by administering these β-lapachone/lipiodol and taxol/lipiodol formulations to mice without toxic side effects. *See*, Pardee page 21, line 7 – page 24, line 8; Figures 2-7. The prior art must contain a suggestion or motivation to combine the prior art references in such a way as to achieve the claimed invention. *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). This motivation to modify the prior art must flow from some teaching in the art that suggests the desirability or incentive to make the modification needed to arrive at the claimed invention. *In re Napier*, 34 U.S.P.Q.2d 1782, 1784 (Fed. Cir. 1995). The mere fact that the prior art could be modified does not make the modification obvious unless the prior art suggests the desirability of the modification (Emphasis Added). *In re Laskowski*, 10 U.S.P.Q.2d 1397, 1399 (Fed. Cir. 1989). The teachings of the primary reference, Pardee, described *supra* do not suggest any desirability of modification as these teachings clearly state that solubilization and therapeutic effectiveness of β-lapachone in lipiodol solved a long standing problem in the art (β-lapachone insolubility). The fact that any modifications made to the prior art may be routine, as suggested by the Examiner in the Office Action at page 3 (Applicants submit *infra* that modifications in the instant case are not routine), is immaterial without any desirability of modification, which is not present in the primary reference, Pardee, which teaches away from any desire to modify since it has solved a long standing problem in the art.

However, irrespective of that assertion which has been found unpersuasive by the Examiner, Applicants further submit that even if one skilled in the art was motivated to solubilize β-lapachone in another solubilizing carrier molecule (they would not), the skilled artisan would not be motivated to combine Pardee and Bodor to reach the present invention.

The Examiner asserts that the skilled artisan would combine Pardee and Bodor to reach the present invention because of the related biological activity of β-lapachone and paclitaxel disclosed in Pardee and the compounds disclosed in Bodor (anti-neoplastic/anti-tumor activity). This is incorrect. One of ordinary skill in the art would readily recognize that biological activity is not a determinate of whether a water-insoluble compound (*e.g.*, β-lapachone, paclitaxel, etc.) would complex with a solubilizing carrier molecule (*e.g.*, beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin); but rather, would recognize that it is the chemical structure and chemical properties of

the water-insoluble compound that are the key determinates to be considered in determining complexation and resulting solubilization of the water-insoluble compound in the solubilizing carrier molecule. Thus, in the instant claimed invention, it is the chemical structure and chemical properties of β-lapachone and the compatibility of those features with the beta-cyclodextrin molecule that will determine the solubility of the complex and its therapeutic utility. *See*, Reddy Declaration ¶ 7.

β-lapachone (3,4-dihydro-2,2-dimethyl-2H-naphtho [1,2-b]pyran-5,6-dione) is a member of the quinone family of molecules and is derived from the napthoquinone, lapachol. β-lapachone has the following chemical structure:



Studies have indicated that several features of the β-lapachone chemical structure are critical to its water solubility; such as, β-lapachone is a molecule having an angular ring system and β-lapachone contains a ortho-quinone system at positions 5 and 6 and a ether linkage at position 2 (Nasonghla et al., *Pharm Res.* 20(10):1626-33, 2003). Therefore, it is the interaction between these critical structural features of the β-lapachone molecule and the essential solubilizing features of the beta-cyclodextrin molecules that will determine the possibly solubility of the formed complex and its resulting therapeutic utility. *See*, Reddy Declaration ¶ 8.

Cyclodextrins are oligosaccharides containing toroidal, hydrophobic central cavity and a hydrophilic outer surface The most common cyclodextrins are α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin. The main differences between these molecules is the amount of glucopyranose units each contains and the size of the central cavity. The central cavity size is 4.7-5.3 angstroms, 6.0-6.5 angstroms and 7.5-8.3 angstroms for the cyclodextrins, respectively (U.S. Patent No. 6,407,079; Croft et al., *Tetrahedron* 39(9):1417-74, 1983; Nasonghla et al., *Pharm Res.* 20(10):1626-33, 2003).

The central cavity of the cyclodextrin molecule is lipophilic as it is lined with skeletal carbons and ethereal oxygens of glucose residues (Fromming et al., *Cyclodextrins in Pharmacy*, Kluwer Acad. Publ., Dordrecht, 1994; Nasonghla et al., *Pharm Res.* 20(10):1626-33, 2003). The

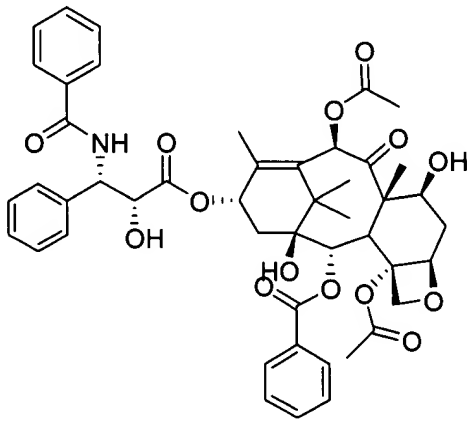
polarity of the cavity is similar to that of aqueous ethanolic solution (Fromming et al., *Cyclodextrins in Pharmacy*, Kluwer Acad. Publ., Dordrecht, 1994). This lipophilic microenvironment is accessible by suitably sized and charged molecules (Nasonghla et al., *Pharm Res.* 20(10):1626-33, 2003). While prediction of compound solubilization by cyclodextrins is highly empirical, it is known that aqueous soluble drugs do not readily complex with cyclodextrins (Nasonghla et al., *Pharm Res.* 20(10):1626-33, 2003). This is the result of specific thermodynamic parameters that must be met for cyclodextrin/drug complexation (Rekharsky et al., *J. Phys. Chem.* 98:4098-4103, 1994; Rekharsky et al., *J. Phys. Chem.* 98:10282-88, 1994; Rekharsky et al., *J. Am. Chem. Soc.* 117:8830-40, 1995). Specifically, it appears that main driving force for complex formation is the release of enthalpy-rich water from the cyclodextrin cavity rendering an environment suitable for hydrophobic, non-aqueous soluble drugs (Mendard et al., *Drug Dev. Ind. Pharm.* 16:91-113, 1990). However, it also appears that for drug-cyclodextrin complexation other forces; such as, van der Waals interactions, hydrogen bonding, hydrophobic interactions, release of cyclodextrin ring strain and solvent-surface tension changes other forces are important (Nishijo et al., *J. Pharm. Sci.* 80:58-62, 1990; Cramer, *Angew. Chem.* 68:115-120, 1956; Tong et al., *Pharm. Res.* 8:951-57, 1991; Jones et al., *Acta Pharm. Technol.* 30:213-23, 1984; Tabushi et al., *J. Am. Chem. Soc.* 100:916-19, 1978; Orstan et al., *Int. J. Pharm.* 80:243-51, 1993). *See*, Reddy Declaration ¶ 8.

Thus, it is clear that the interaction between the chemical structure and properties (*e.g.*, geometry, hydrophobicity, etc.) of the water-insoluble drug (*e.g.* β-lapachone or analogs and derivatives thereof, paclitaxel, etc.) and the cyclodextrin molecule (*e.g.* beta-cyclodextrin molecules) and the compatibility of the drug to satisfy these parameters of the cyclodextrin molecule are critical to determine if the solubility of drug of interest can be enhanced by complexation with the cyclodextrin molecule. *See*, Reddy Declaration ¶ 8.

Applicants submit that based on the foregoing essential chemical properties of β-lapachone and beta-cyclodextrin molecules and the requirements for the complexation and successful solubilization of β-lapachone with beta-cyclodexrin molecules, one of ordinary skill in the art would not be motivated to combine Pardee and Bodor. Specifically, the Examiner asserts that the skilled artisan would combine Pardee and Bodor because Bodor contemplates at least 57 anti-tumor agents which can be solubilized in hydroxypropyl-beta-cyclodextrin and β-lapachone is a water-insoluble, anti-tumor compound. *See*, Office Action at page 4. Applicants disagree.

The skilled artisan reading Bodor would recognize that none of the contemplated anti-tumor compounds disclosed therein are members of the ortho-quinone family of molecules or derived from napthoquinones. Further, while a few compounds have an angular ring system (*i.e.*, meogarol, homoharringtonine, levonantradol, vincristine, vinblasine) and a few other compounds have an ether linkage, albeit in a sugar moiety (*i.e.*, Ara-AC, Ara-C, dihydro-5-azacytidine, tiazofurin, sangivamycin, cytosine arabinoside, 6-mercaptopurine, etoposide and teniposide), none of the contemplated anti-neoplastic compounds of Bodor have an ortho-quinone system and certainly none of the disclosed compounds comprise all the structural features essential to the water-solubility of β-lapachone (angular ring system, ortho-quinone system and a ether linkage). *See*, Reddy Declaration ¶ 9 and Appendix A.

Thus, based on the lack of structural similarity between the compounds of Pardee and the compounds of Bodor, the only suggestion or motivation to combine Pardee and Bodor is the anti-neoplastic activity of the disclosed compounds, which, as described in the prior art, is not determinative of drug/carrier complexation or solubilization potential. In fact, the prior art teaches that not all compounds with anti-neoplastic activity can be solubilized and therapeutically effective when complexed with beta-cyclodextrin molecules. For example, Pardee discloses two compounds which are water-insoluble and have anti-tumor biological activity, β-lapachone and paclitaxel, and further teaches that these two compounds are readily solubilized and therapeutically effective when complexed with lipiodol. While paclitaxel is water-insoluble and has anti-neoplastic/anti-tumor activity similar to β-lapachone, these compounds have very different chemical structures. *See*, Reddy Declaration ¶ 10. The chemical structure of β-lapachone is shown above and paclitaxel has the following chemical structure:



Based on the Examiner's assertion that it would be obvious to solubilize water-insoluble, anti-neoplastic/anti-tumor agents in beta-cyclodextrin molecules based on the combination of Pardee and Bodor, one would expect paclitaxel to be readily solubilized and therapeutically effective when complexed to beta-cyclodextrin molecules, similar to β-lapachone since both compounds are water-insoluble and have anti-neoplastic/anti-tumor activity, even though they have different chemical structures. This is not the case as studies have shown that paclitaxel, a water-insoluble, anti-neoplastic/anti-tumor agent, is not solubilized and therapeutically effective in beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin (Nasonghla et al., *Pharm Res.* 20(10):1626-33, 2003). As only one of the two water-insoluble, anti-neoplastic/anti-tumor compounds disclosed in Pardee is solubilized and therapeutically effective in beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin disclosed by Bodor, Applicants submit that there is no suggestion or motivation to combine Pardee and Bodor and that one of ordinary skill in the art would recognize that the combination of Pardee and Bodor would not render a reasonable expectation of success. *See*, Reddy Declaration ¶ 10.

Moreover, Applicants submit that Bodor teaches away from the present invention. As stated in Applicants' June 3, 2004 response, of the myriad of water-insoluble, anti-neoplastic compounds known in the art, Bodor merely contemplates approximately 57 compounds and only provides working examples for solubilizing only four (Methotexate, Chlorambucil, Lomustine and Melphalan) in hydroxypropyl-beta-cyclodextrin. *See*, Col. 76, lines 44-49; Col. 77, Table III; Col. 76, line 65 – Col. 79, line 44 including Tables V – VIII. The Examiner stated the fact that only these specific species are used in the working examples is not evidence, in and of itself, of any limitations of the prior art teachings, because a patent is not limited to its working examples but instead must be considered for the entirety of what it discloses. *See*, Office Action at page 4. Applicants submit that besides these four working examples, the remaining anti-neoplastic compounds disclosed in Bodor are purely prophetic and that, in fact, several of these contemplated anti-neoplastic compounds are not readily solubilized in beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin (*i.e.*, desmethylmisonidazole, Ara-C, hydroxyurea, 5-fluorouracil, 6-mercaptopurine, 5-methylthtrahydrohomofolic acid, SR-2555, SR-2580, bactobolin, acivicin, streptozotocin). Specifically, these compounds are known in the art to be water-soluble; *See*, Reddy Declaration ¶ 11 and Appendix B, and as described *supra*, the lipophilic microenvironment of the beta-cyclodextrin molecule is accessable by suitably sized and charged molecules and that water-soluble drugs do not

readily complex with cyclodextrins due to specific thermodynamic parameters that must be met for cyclodextrin/drug complexation (Rekharsky et al., *J. Phys. Chem.* 98:4098-4103, 1994; Rekharsky et al., *J. Phys. Chem.* 98:10282-88, 1994; Rekharsky et al., *J. Am. Chem. Soc.* 117:8830-40, 1995; Nasonghla et al., *Pharm Res.* 20(10):1626-33, 2003). Applicants submit that this data shows that several species of the genus of anti-neoplastic compounds disclosed in Bodor are unable to complex and enhance their solubility with beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin molecules and is evidence that the skilled artisan in view of the prior art would readily recognize the limitations of the teachings of Bodor and would restrict those teachings to only the enhanced solubility of Methotexate, Chlorambucil, Lomustine and Melphalan in hydroxypropyl-beta-cyclodextrin as described in the working examples. *See*, Reddy Declaration ¶ 11.

For the foregoing reasons, Applicants submit that there is no suggestion or motivation to combine Pardee and Bodor to reach the present invention

Unexpected Results:

Applicants stated in their June 3, 2004 response that the present invention discloses that combining, mixing, and/or complexing β-lapachone with hydroxypropyl-beta-cyclodextrin surprisingly improves the stability of β-lapachone to photoreduction and shows that the solubility of β-lapachone increases linearly with the increase in hydroxypropyl-beta-cyclodextrin concentration.

Applicants submitted that these results described in the specification demonstrate that the claimed invention displays the surprising, unexpected and superior stability of a pharmaceutical composition comprising a therapeutically effective amount of β-lapachone solubilized by beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin and that these results were not taught or suggested by either Pardee or Bodor alone or in combination.

The Examiner states he does not agree that the linear relationship observed between solubility and increase in hydroxypropyl-beta-cyclodextrin concentration is unexpected. *See*, Office Action at pages 4-5. Applicants disagree and submit that the complexation of β-lapachone with beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin was expected to produce a typical B-type phase solubility curve (Higuchi and Connors, *Adv. Anal. Chem. Instrum.* 4:117-212 (1965)) and not the A1-type phase solubility curve that was actually produced, which denoted the surprising linear increase in solubility. In fact, studies have shown that when β-lapachone is complexed with alpha-cyclodextrin, beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin or gamma-cyclodextrin only

complexation with beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin resulted in linear increases in solubility which resulted in therapeutic effectiveness. Nasonghla et al., *Pharm Res.* 20(10):1626-33, 2003. Thus, Applicants submit that the skilled artisan would readily recognize based on the teachings in the art that the varied relationship observed between drug solubility and increase in solubilizing carrier concentration among members of the cyclodextrin family show that the linear relationship observed between solubility and increase in beta-cyclodextrin and hydroxypropyl-beta-cyclodextrin concentration is unexpected. *See*, Reddy Declaration ¶ 12.

The Examiner also states that he agrees that the improved stability of β-lapachone and hydroxypropyl-beta-cyclodextrin complexes is unexpected. However, the Examiner states that the instant claims are not commensurate in scope with the evidence presented therein as the claims are drawn not only to hydroxypropyl-beta-cyclodextrin but broadly drawn to beta-cyclodextrin. Further, the Examiner suggest Applicants amend the claims to include a functional limitation to limit the claims to be commensurate in scope with the evidence of unexpected results. *See*, Office Action at pages 4-5.

Applicants submit that the teachings in the art in combination with the evidence presented in the instant application show that the evidence in the specification is not applicable only to hydroxypropyl-beta-cyclodextrin but also to beta-cyclodextrin. Specifically, hydroxypropyl-beta-cyclodextrin is obtained by treating a base-solubilized solution of beta-cyclodextrin with propylene oxide thereby modifying the hydrophilic outer surface which increases aqueous solubility well in excess of 60% (w/v). Pitha et al., *Int. J. Pharm.* 29:73-82, 1986. As described *supra*, it is the central, lipophilic cavity of the cyclodextrin molecule that is critical for the complex formation between the cyclodextrin molecule and the water-insoluble drug candidate (Fromming et al., *Cyclodextrins in Pharmacy*, Kluwer Acad. Publ., Dordrecht, 1994; Rekharsky et al., *J. Phys. Chem.* 98:4098-4103, 1994; Rekharsky et al., *J. Phys. Chem.* 98:10282-88, 1994; Rekharsky et al., *J. Am. Chem. Soc.* 117:8830-40, 1995) and recent studies have shown it is the interaction of the drug candidate and the central cavity of the cyclodextrin molecule which results in drug stability. Nasonghla et al., *Pharm Res.* 20(10):1626-33, 2003. As the structure of the inner cavity is unchanged by the treatment of beta-cyclodextrin with propylene oxide and modification of the hydrophilic outer surface to produce hydroxypropyl-beta-cyclodextrin, one of ordinary skill in the art would readily recognize that complexation of β-lapachone in either beta-cyclodextrin or

hydroxypropyl-beta-cyclodextrin, which share identical central cavity structural parameters, surprisingly improves the stability of β-lapachone to photoreduction. *See*, Reddy Declaration ¶ 13.

Further, the claims in the instant application are drawn to compositions of matter, and as such, these compositions inherently comprise the unexpected and superior properties described above (*e.g.*, improved stability of β-lapachone to photoreduction and that the solubility of β-lapachone increases linearly with the increase in beta-cyclodextrin concentration). Therefore, Applicants submit the pending claims are commensurate in scope with these unexpected and superior properties and do not require the addition of the functional limitation suggested by the Examiner.

For the foregoing reasons, the combination of Pardee and Bodor could not lead the ordinarily skilled artisan to the unexpected and superior advantages (increased stability of β-lapachone) that the claimed invention provides.

Reasonable Expectation of Success:

Applicants maintain that the Examiner has not applied the *prima facie* case of obvious standard as required by MPEP § 2143 and has engaged in impermissible hindsight reconstruction to arrive at the present rejection because there is no suggestion or motivation to combine Bodor and Pardee with a reasonable expectation of success, as described *supra*.

The Examiner asserts that motivation exists to engage in routine experimentation to find alternative solubilizing agents for β-lapachone despite the fact that β-lapachone had been solubilized in lipiodol in Pardee, solving a long-felt but unsolved need in the art (*i.e.*, problem of β-lapachone insolubility). *See*, Office Action at pages 2-4. Specifically, the Examiner states that solving this long felt need in the art does not mean that the skilled artisan would be foreclosed from additional routine experimentation. *See*, Office Action at page 2, ¶5.

It appears that the Examiner is suggesting that since β-lapachone is water-insoluble it would be obvious for one of ordinary skill in the art to use any solubilizing carrier molecule to render β-lapachone soluble in water. This is clearly a rejection based on an obvious-to-try standard which is not permitted.

The admonition that obvious to try is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been obvious to try would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful

result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.... In others, what was obvious to try was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it (Emphasis Added). *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

The only motivation or guidance in the prior art that the Examiner has asserted is that additional solubilizing agents could be tried under the rubric of routine experimentation. Specifically, the Examiner states that Bodor provides simple tests for determining the usefulness of hydroxypropyl-beta-cyclodexrin in solubilizing various poorly soluble drugs, including various anti-neoplastic agents. *See*, Office Action at page 2, ¶5. In making this assertion, Applicants submit the Examiner is engaging in impermissible hindsight reconstruction.

The "as a whole" instruction in 35 U.S.C. § 103 prevents evaluation of the invention part by part. *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270 (Fed. Cir. 2004). Without this important requirement, an obviousness assessment might break an invention into its component parts (A + B + C), then find a prior art reference containing A, another containing B, and another containing C, and on that basis alone declare the invention obvious. *Id.* This form of hindsight reasoning, using the invention as a roadmap to find its prior art components, would discount the value of combining various existing features or principles in a new way to achieve a new result - often the very definition of invention. *Id.* Thus, there must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor (Emphasis Added). *Id.* When the patented invention is made by combining known components to achieve a new system, the prior art must provide a suggestion or motivation to make such a combination. *Id.*

Using references available on the filing date of the instant application, an innumerable amount of solubilizing agents are potentially useful for solubilizing water-insoluble, anti-neoplastic agents; including but not limited to, polyethylene glycol, cremephor EL, poly-L-gultamic acid, polyoxyethylene hardened castor oil, polysorbate 80, nicotinamide, polyoxyethylenesorbitan monolaurate, Macrogol and castor oil fatty acid ethyl ester (Badary, et al. *Anticancer Drugs*.

9(9):809-15, 1998; Das et al. *J. Biomed. Mater Res.* 55(1):96-103, 2001; Zou et al. *Int J Oncol.* 18(2):331-6, 2001 and U.S. Patent No. 5,846,969.

Based on the teachings in the art, the skilled artisan would recognize that the experimentation necessary to find and use the cyclodextrins of the Bodor reference with the β-lapachone compounds of the Pardee reference would have not been routine. In fact, to use the simple tests of Bodor referred to by the Examiner, without the teachings of the instant application, one of ordinary skill in the art would have to try most or all of the available agents recognized for solubilizing neoplastic agents and following the test in *In re O'Farrell* to try each of numerous possible choices until one possibly arrived at a successful result an impermissible standard for assessing obviousness (853 F.2d 894, 903). Applicants submit that reaching the claimed invention without the teachings of the instant application would involve more than routine experimentation, and for each agent tested, would not have a reasonable expectation of success, as described in detail *supra*. Moreover, there is no specific suggestion or motivation within Pardee and Bodor or within the nature of the problem to be solved (Pardee solved the long standing problem in the art) to solubilize β-lapachone with beta-cyclodextrin, which is required under the test of *Ruiz* (357 F.3d 1270).

Therefore, Applicants submit that one of ordinary skill in the art would have no reasonable expectation of success combining the teachings of Pardee and Bodor to reach the presently claimed invention. *See*, Reddy Declaration ¶ 14.

Applicants respectfully request the § 103 rejection be withdrawn.

CONCLUSION

In view of the aforementioned remarks and amendments, the Applicants believe that each of pending claims is in condition for allowance. Reconsideration, withdrawal of the rejections, and passage of the case to issue is respectfully requested. A notice to this effect is earnestly solicited.

If, upon receipt and review of this amendment, the Examiner believes that the present application is not in condition for allowance and that changes can be suggested which would place the claims in allowable form, the Examiner is respectfully requested to call Applicant's undersigned counsel at the number provided below.

Respectfully submitted,

Matthew Rogers Reg. No. 59572

Ivor R. Elrifi, Reg. No. 39,529
Attorney for Applicant
c/o Mintz, Levin
Telephone 617/542-6000
Fax: 617/542-2241
Customer No.: 30623

Dated: November 30, 2004

TRA 1969522v1